Cancer of the lung in women

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Harley, H. R. S. (1976). *Thorax*, 31, 254-264. **Cancer of the lung in women.** A study from Wales of 132 women with cancer of the lung admitted consecutively during the five years 1964-68, and of 13 other women submitted to surgery at an earlier period, showed that the prognosis for women was worse than for men. Every woman except one was followed up for more than five years. Of the 132 women in the consecutive series only five survived for five years, while the five-year survival rate after resection in 35 women was less than one-half of that for men.

The cause of the worse prognosis for women in Wales appears to be due to some sex-linked factor. It cannot be explained by the age of the patient or by the histology, location, early aggressiveness or resectability of the growth. The prognosis of cancer of the lung in English, French, and American women is considered.

The relative incidence of the disease in women and men is discussed. Sex and nationality appear to be of importance, but the influence of tobacco and other atmospheric carcinogens is obscure.

During the five-year period 1964-68 inclusive 978 patients were admitted to Sully and Llandough Hospitals, Cardiff with cancer of the lung. Of these, 846 (86.5%) were men and 132 (13.5%) were women, giving a sex ratio of 6.4 : 1. A complete analysis of all aspects of the 132 women was made and some of this analysis is presented. In addition, 13 women studied in a previous analysis of 237 consecutive patients operated upon for cancer of the lung were added to those treated surgically, making a total of 50 women so treated. All figures given in the following analysis, unless otherwise stated, apply only to the 132 women referred to above. The average age of the women was 58.4 years, with a range of 35-76 years.

This group of women smoked considerably less than men previously studied by the writer; 22.4% of the women did not smoke and 39.6% either did not smoke or smoked less than 10 cigarettes per day.

The location of the tumours is similar to that in men. The tumours were more commonly located in the upper than in the lower lobes and on the right side than on the left side, because of the presence of the middle lobe and the frequency of main bronchus tumours on the right side. Main bronchus tumours were more than twice as common on the right side as on the left side. The incidence of peripheral circumscribed tumours

TABLE I
NUMBER OF CIGARETTES SMOKED PER DAY BY 116 OUT OF 132 WOMEN WITH CANCER OF THE LUNG IN WHOM SUFFICIENT DATA WERE AVAILABLE

No. of Cigarettes smoked	No. of Women	Percentage
None	26	22.4
Less than 10	20	17.2
10 to 15	28	24.1
16 to 20	23	19.8
21 or more	19	16.4
Total	116	99.9

was only 16.7%; this is lower than that given by other writers. In the far east, peripheral tumours account for about 50% of cases whereas in European countries the proportion is only about 25% (Belcher, 1971).

The histopathology was ascertained in 103 of the women and is shown in accordance with the World Health Organization classification in Table II. Especially to be noted are the low percentage of epidermoid tumours and the high percentages of oat-cell tumours and of adenocarcinomata relative to their incidence in men. Oat-cell tumours are somewhat more common than the other two. Goldman (1965), analysing patients

TABLE II
HISTOPATHOLOGY OF 103 CASES OF CANCER OF THE LUNG IN WOMEN

Histology	No. of Cases	Percentage
Type I (epidermoid)	29	28.5
Type II (small-cell anaplastic)	37	35.9
II 1 (fusiform)	0	0.0
II 2 (polygonal)	2	1.9
II 3 (oat)	33	32.0
II 4 (others)	2	1.9
Type III (adenocarcinoma)	28	27.2
III 1a (acinar)	21	20.4
III 1b (papillary)	6	5.9
III 2 (bronchioloalveolar)	1	1.0
Type IV (large-cell)	6	5.8
IV 1 (solid with mucin)	5	4.95
IV 2 (solid without mucin)	1	1.0
IV 3 (giant-cell)	0	0.0
IV 4 (clear-cell)	0	0.0
Other types	3	2.9
V+undifferentiated	1	1.0
IX 3 (carcinosarcoma: pleomorphic)	1	1.0
Completely necrotic	1	1.0
Total	103	

from the same area as the writer, found that epidermoid carcinomata accounted for 39.3% of lung cancers in men but for only 11.4% of those in women. On the other hand, the cancers were oat-celled in 20.1% of men as against 52.3% of women, and the corresponding figures in the two sexes for adenocarcinoma were 6.8% and 9.1%. A relatively high proportion of adenocarcinoma in women has been reported by many workers (Christiansen, 1953; Jacobsen, 1953; Wynder *et al.*, 1956; Haenszel, Shimkin, and Mantel, 1958; Kreyberg and Saxén, 1961; Ederer and Merscheimer, 1962; Kreyberg, 1962; Vincent, Satterfield, and Ackerman, 1965; Ashley and Davies, 1969; Merlier, Goux, and Hummel, 1969; Deaner and Trummer, 1970; Beamis, Stein, and Andrews, 1975). Jacobsen (1953), Christiansen (1953), Kreyberg and Saxén (1961), Kreyberg (1962), Vincent *et al.* (1965), and Merlier *et al.* (1969) found it to be the commonest histological type in women. Haenszel *et al.* (1958) noted a marked variation in the ratio of squamous to undifferentiated tu-

mours in women in various centres, but the proportion of adenocarcinomata was fairly constant at about 37.3%. Many workers have also found a lower percentage of epidermoid carcinoma in women than in men, and some a higher percentage of undifferentiated carcinoma (Goldman, 1965; Ashley and Davies, 1969; Kennedy, 1973; Lemoine and Fauvet, 1974). Deeley (1975) found that the tumours were oat-celled in 40% of women as against 18% of men, while the corresponding percentages of squamous-celled carcinoma were 30 and 61.

Table III shows the relation between smoking and the three common cytological types of cancer. The high incidence of non-smokers with adenocarcinoma is notable (40.7%) and so, to a lesser extent, is the smoking of less than 10 cigarettes per day. The lowest incidence of non-smoking was in patients with oat-cell tumours.

The percentages of tumours of the three common histopathological types which occupied a main bronchus or the periphery of the lung are

TABLE III
RELATION OF SMOKING TO THE THREE COMMON HISTOPATHOLOGICAL TYPES OF CANCER OF THE LUNG IN 89 OF THE 103 WOMEN WITH PROVEN CYTOLOGY

Cytological Type	Number	Non-smokers	Percentage Non-smokers	Smoked less than 10 per day	Percentage smoking	
					Less than 10 per day	More than 10 per day
Epidermoid	29	4	13.8	4	13.8	65.5
Oat-cell	33	2	6.1	2	6.1	78.8
Adenocarcinoma	27	11	40.7	5	18.5	29.6
Total	89	17	19.1	11	12.35	69.9

TABLE IV
PERCENTAGE OF THE THREE COMMON HISTOPATHOLOGICAL TYPES OF CANCER WHICH OCCUPIED
A MAIN BRONCHUS OR THE PERIPHERY OF THE LUNG

Situation	Cytological Type	Total No. of Cytological Type in Series	Occurring peripherally or in a Main Bronchus	
			No.	%
Main bronchus	Epidermoid	29	10	34.5
	Oat-cell	33	13	39.4
	Adenocarcinoma	27	2	7.4
Peripheral	Epidermoid	29	4	13.8
	Oat-cell	33	4	12.1
	Adenocarcinoma	27	8	29.6

shown in Table IV. Noteworthy are the high percentages of epidermoid and oat-cell tumours in a main bronchus and of adenocarcinoma at the periphery. This correlates well with the percentage of positive bronchoscopic biopsy findings in the three types of tumour. A positive diagnosis was made in 55.2% of epidermoid tumours, in 48.5% of oat-cell tumours, and in only 14.9% of adenocarcinomata. A relatively high proportion of adenocarcinomata occurring at the periphery has been noted by other workers (Spencer, 1962; Hanbury, 1964; Merlier *et al.*, 1969; Belcher, 1971). Bronchoscopy was performed on 88 of the women (66.7%), biopsy specimens were taken in 56.8% of these (50 patients), and the findings were positive cytologically in 80% of the biopsies (40 patients). The sputum was examined for malignant cells in 75 of the 132 patients (56.8%). Malignant cells were found in 18 of these (24%) and suspicious cells in three others (4%).

Lymphatic and haematogenous dissemination and direct spread to the chest wall and intrathoracic structures were prominent features of these cases. Thus in 17.4% of the women there was spread to the extrathoracic nodes and in 25% there were haematogenous metastases at the time of admission to hospital, demonstrating the gravity of cancer of the lung in women. No less than 51 women (37.9%) had one or both of these forms of metastases. Furthermore, 32 of the patients (24.2%) had malignant pleural effusions, while spread to surrounding structures had occurred in 36 women (27.3%).

Ashley and Davies (1969), working elsewhere in South Wales, found a higher percentage of extrathoracic spread in women than in men. They found such spread in 18 out of 56 women at the time of diagnosis, whereas the expected number for men matched for histological type would have been seven. On the other hand, Ederer and Merseimer (1962) and Watson and Schottenfeld (1968), reporting on large numbers of patients

studied in the USA, found no difference in the spread of the disease in men and women, while Hanbury (1964), working in London, found at necropsy that the spread of the disease in 43 women was similar to that of carcinoma of the bronchus in general, except for a high incidence of skeletal involvement and a low incidence of renal metastases.

The extreme gravity of cancer of the lung in these women is highlighted by the overall survival rate (Table V). As can be seen, all but three of the women who were followed up died during the 5- to 10-year period of observation, though five were still alive at five years. The survival period was determined in 127 out of the 128 women who died. The average period of survival was only 7.9 months.

TABLE V
OVERALL SURVIVAL OF 132 WOMEN WITH CANCER OF
THE LUNG FOLLOWED UP FOR 5 TO 10 YEARS

Not followed up	1
Dead	128
Alive	3
Total	132

TREATMENT

The results in the different treatment groups are shown in the tables and text which follow.

RESULTS IN 39 WOMEN WHO RECEIVED NO TREATMENT The results in this group are shown in Table VI. The patient shown as alive and well at 10 years had a well-differentiated epidermoid carcinoma of the left upper lobe proved by bronchoscopic biopsy. Her respiratory function was considered to be too poor to permit thoracotomy. Only four patients survived for 12 months and

TABLE VI
RESULTS IN 39 WOMEN WITH CANCER OF THE LUNG
WHO RECEIVED NO TREATMENT

Not followed up	1
Alive and well (after 10 years)	1
Dead	37
Total	39

none survived for three years. The average survival period from admission to death was 4.8 months and the longest period was 2 years 8 months.

RESULTS IN 16 WOMEN TREATED WITH DEEP X-RAY THERAPY (DXT) The results in this group are shown in Table VII. The average period between radical deep x-ray therapy and death was 9.2 months and the longest period was 2 years 9 months. Although none of these patients was cured by radical deep x-ray therapy the average survival period was nearly twice as long as for those who received no treatment (4.8 months). Merlier *et al.* (1969) noted improved survival when resection was followed by cobalt therapy. My radiotherapy colleague, Dr. T. J. Deeley, now has an overall four-year survival rate of 8% (personal communication). His rates for epidermoid tumours, adenocarcinoma, oat-cell tumours, and anaplastic tumours are 10%, 11%, 6%, and 6% respectively, while the four-year survival rate for patients with involved neck glands is 7%. It must be stressed that these figures relate to all cases of cancer and not only to women.

TABLE VII
RESULTS OF DEEP X-RAY THERAPY IN 16 WOMEN WITH
CANCER OF THE LUNG FOLLOWED UP FOR 5 TO 10 YEARS

Type of DXT	Alive	Dead	Total
Radical to primary tumour	0	9	9
Palliative to primary tumour or metastases	0	7	7
Total	0	16	16

The average period of survival after palliative deep x-ray therapy was 3.5 months and the longest period was 7.0 months. These figures are worse than for those who received no treatment. While palliative deep x-ray treatment may relieve symptoms it does not appear to prolong life.

RESULTS IN 40 WOMEN TREATED PRIMARILY WITH CHEMOTHERAPY All the patients in this group died during the period of observation. Every patient whose date of death was known died within three years of starting treatment, and 94.9% of them died within 12 months. Their average period of survival was 4.7 months and the longest period was 2 years 6 months. These figures are almost the same as for those who received no treatment. Three of the patients were submitted to thoracotomy before chemotherapy, and one of these had deep x-ray therapy and chemotherapy simultaneously. Two other patients had deep x-ray therapy after chemotherapy for painful secondary deposits in one and for superior vena caval obstruction in the other. A number of chemotherapeutic agents were used, the most frequent being nitrogen mustard (intravenously, 20 cases) and cyclophosphamide (18 cases). These agents appear to have had no influence in prolonging life. Modern combinations of multiple therapeutic agents were not employed.

RESULTS OF POUDRAGE FOR MALIGNANT PLEURAL EFFUSION IN SIX WOMEN All six women died during the period of observation. The average period between poudrage and death was 4.0 months and the longest period was 7.0 months. Although poudrage does not prolong life it is effective in controlling the reaccumulation of effusion and makes the patient's remaining days more comfortable. Of the six women treated by this procedure, two died so soon after (one and two days respectively) that its effectiveness in controlling the reaccumulation of liquid cannot be assessed. Of the remaining four women, two lived for five months and two for seven months after poudrage. Three of these four women required no aspirations after the procedure, and in the case of the one examined *post mortem* no effusion was found. The remaining patient, who survived seven months after poudrage, was readmitted four days before she died with a recurrent effusion. Aspiration, the first one done since the poudrage, removed 550 ml of dirty brown liquid.

RESULTS OF SURGICAL TREATMENT Thirty-seven of the 132 women in this series were selected for surgery. To these are added the 13 other women referred to earlier, making a total of 50 women submitted to surgery. Among the 132 women in the present series, seven (5.3%) were submitted to thoracotomy, their growths being found to be inoperable, while 30 women (22.7%) had their

TABLE VIII
HISTOLOGY OF LUNG CANCER IN 50 WOMEN SUBMITTED TO SURGERY

Histology	Surgery	Thoracotomy	Resection	Survived 5 Years
Epidermoid	11	3	8	1
Small-cell anaplastic				
Oat-cell	17	8	9	1
Others	1		1	
Adenocarcinoma	14	2	12	3
Bronchioloalveolar	1		1	
Large-cell (IV 1)	2		2	
Type V+ undifferentiated	1		1	
Carcinosarcoma	1		1	
Not known	2	2		
Total	50	15	35	5

growths resected, 14 by lobectomy, 15 by pneumonectomy, and one by resection of the apical and posterior segments of the upper lobe. Of the other 13 patients, eight had thoracotomy alone while five had their growths resected, one by lobectomy and four by pneumonectomy. The histopathology of the cases submitted to surgery, together with the five-year survivals after resection, are shown in Table VIII, and the operations performed in Table IX. Analysis of the 132 women in the main series showed that resection was carried out in six of the 29 epidermoid cancers (20.7%), in six of the 33 oat-celled cancers

to those for the group who had no treatment or who were treated by chemotherapy or palliative deep x-ray treatment.

TABLE X
RESULTS OF THORACOTOMY IN 15 WOMEN WITH
CANCER OF LUNG FOLLOWED UP FOR 5 TO 20 YEARS

Alive	0
Dead	14
Lost to follow-up	1
Total	15

TABLE IX
OPERATIONS PERFORMED ON 50 WOMEN WITH CANCER
OF LUNG FOLLOWED UP FOR 5 TO 20 YEARS

Surgery	Number	Percentage
Thoracotomy	15	30.0
Resection	35	70.0
Pneumonectomy	19	
Lobectomy	15	
Segmental resection	1	
Total	50	100.0

(18.2%), and in 12 of the 27 adenocarcinomas (44.4%). The resection rate was thus more than twice as great for adenocarcinoma as for the other two varieties. This is probably due to the fact that a high proportion of the adenocarcinomas were peripherally situated (Table IV). The results of the 15 patients who had thoracotomy only are shown in Table X. Every patient died within nine months, over 90% within six months. The average period of survival after thoracotomy was 4.1 months, and the longest period was 9.0 months. These figures are similar

The results following resection are shown in Tables VIII, XI and XII. The asterisk in Table XII shows a five-year survival rate of only 14.3%. One of those surviving at five years died of cancer at five years one month. If she is excluded from the five-year survival rate then the rate becomes only 11.4%. This is a much lower survival rate than for men (in this region approximately 25%). The usual figures for survival given in the literature take no cognisance of sex and are, therefore, heavily weighted in favour of men. The five-year survival rates given in the different reports quoted by Belcher and Anderson (1965) range between 20.5 and 33.0%, most between 25.0 and 33.0%.

TABLE XI
RESULTS OF RESECTION IN 35 WOMEN WITH CANCER
OF LUNG FOLLOWED UP FOR 5 TO 20 YEARS

Alive and well (at 5½ and 8 years)	2
Dead	33
Total	35

TABLE XII

SURVIVAL PERIOD AFTER RESECTION OF LUNG CANCER
IN 35 WOMEN FOLLOWED UP FOR 5 TO 20 YEARS

	No.	%
Died within 3 months	10	31.7
6 months	13	37.1
12 months	19	54.3
2 years	23	65.7
3 years	26	74.3
4 years	28	80.0
5 years	*30	*85.7
6 years	32	91.4
7 years	33	94.3
Alive and well (at 5½ and 8 years)	2	5.7
Total	35	

*See text.

Only five of the 132 women (3.8%) in the main series, and one of the 13 women in the small series, survived five years, making a total of six survivors at five years. One, alive and well at 10 years, despite having received no treatment, had a well-differentiated squamous-cell carcinoma, proved by bronchoscopic biopsy. The other five had their growths resected (Table VIII), two by pneumonectomy and three by lobectomy. One of these had a squamous-celled carcinoma of moderate differentiation and was alive and well at five years six months after lobectomy. One had an oat-cell carcinoma and died of carcinomatosis seven years after pneumonectomy. Three had adenocarcinoma, two acinar and one papillary. One of these, with a well-differentiated adenocarcinoma (type III 1a), died of carcinoma five years one month after lobectomy; the second, with a well-differentiated adenocarcinoma (type III 1a), died of pneumonia 5 years 10 months after pneumonectomy; and the third, with a papillary adenocarcinoma of moderate differentiation, was alive and well eight years after lobectomy. Thus of the six survivors at five years five had had their growths resected. In two the tumour was an epidermoid carcinoma, in three an adenocarcinoma, and in only one an oat-cell carcinoma. All of the epidermoid and adenocarcinomatous tumours were either well (3) or moderately well (2) differentiated.

The resectability rate for adenocarcinoma was more than twice as great as that for epidermoid and oat-celled carcinoma. The survival rate after resection was also better for adenocarcinoma than for the other two types. Survival for five years after resection occurred in one out of eight women with an epidermoid carcinoma, in one

out of nine with an oat-celled carcinoma, and in three out of 12 with an adenocarcinoma (although one of these three died only one month after the five-year period). The figures are too small to be significant.

DISCUSSION

Discussion will be confined to two subjects, the incidence and prognosis of cancer of the lung in women compared to that in men.

The incidence of cancer of the lung in women is increasing both absolutely and relatively to that in men, at least in Britain (*Lancet*, 1971; Royal College of Physicians, 1971, Kennedy, 1973) and in the USA (Deaner and Trummer, 1970; Burbank, 1972; Wynder, Covey, and Mabuchi, 1973; Beamis *et al.*, 1975). In England and Wales the death rate per million of the population from malignant neoplasms of the trachea, bronchus, and lung between 1960 and 1969 rose in men from 852 to 1040, and in women from 131 to 202 (*Lancet*, 1971). These figures represent percentage increases of 22 and 54 respectively. In the USA mortality rates for cancer of the lung in men showed a rapidly rising incidence until 1960, but a slower rise thereafter. On the other hand, in women the rise in incidence was slow until 1960, but since then it has become more rapid (Beamis *et al.*, 1975). This is well illustrated by the changing sex ratio for deaths from lung cancer in the USA (Wynder *et al.*, 1973; Beamis *et al.*, 1975):

Year	Sex Ratio in favour of Men
1900	Virtually unity
1923	1.03
1930	1.7
1940	2.9
1950	4.5
1960	6.6
1965	6.0
1969	5.1

It can be seen that the sex ratio rose steadily to a peak in 1960, since when it has been declining. Haenszel and Taeuber (1964) made the interesting observation that the sex ratio in non-smokers was only 1.3, no larger than for many causes of death. The figures for sex ratio given by Kennedy (1973) show trends similar to those in the USA for patients in Sheffield, England. The following figures show a steady increase in the number of women with lung cancer admitted during each three-year period and a steady fall in the sex ratio:

	1957-60	1961-64	1965-68	1969-72	Total
No. of women admitted	38	46	75	71	230
Sex ratio	6.1	4.6	3.5	2.4	4.0

The reason for the recent more rapid rise in incidence in women compared with men is not clear. The Royal College of Physicians (1971) related it to increased smoking among women, and Beamis *et al.* (1975) stated that the cause of the increased incidence of carcinoma of the lung in women is smoking women with Kreyberg group I tumours (epidermoid, small-cell, undifferentiated, and large-cell tumours). But if the increase in women is due to increased smoking there should be a change in the proportions of the histological types of cancer, and this has not occurred in either Britain (Kennedy, 1973) or the USA (Beamis *et al.*, 1975). Adenocarcinomas come within Kreyberg's group II tumours (Kreyberg, 1959, 1961) which he believes are not related to irritants, notably tobacco. Kreyberg (1959) also pointed out that a high proportion of adenocarcinomas occur in men in countries where the total incidence of cancer of the lung is low, and stated that the total incidence might be predicted by a knowledge of this proportion alone. These considerations would suggest that the worldwide differences in sex ratio might be due to variations in tobacco consumption. Belcher (1971), however, in an exhaustive investigation of sex ratios in 49 different countries, has amassed evidence that throws doubt on this suggestion.

He found little correlation between sex ratio and total incidence of lung cancer in various countries, while in those countries where there has been a great increase in total incidence of lung cancer, such as Japan, Taiwan, Britain, and America, there has been no decrease in the proportion of adenocarcinomas. He also found a great variation in the sex ratio of different countries, ranging from 13.5:1 in Holland to 1:1 in Nigeria. This difference was due almost entirely to a varying incidence of cancer of the lung in men, the incidence in women being remarkably constant. The sex ratio appeared to be closely related to nationality. The peoples of the world could, with few exceptions, be divided into those of European descent, who had a relatively high sex ratio, and those of non-European descent who had a lower one. Ethnic groups, living in foreign countries, tended to preserve the sex ratio, but not the total incidence, of their country of origin. He found little or no correlation in the different

countries between the sex ratio and either the total consumption of tobacco or economic standards. Gentleman and Forbes (1974), on the other hand, think that smoking does influence the ratio of male to female mortality rates.

It is clear that the cause of the accelerating incidence of the disease in women as compared to men is uncertain. The influence of tobacco is obscure. In men epidermoid, oat-cell, and large-cell cancers have a strong association with smoking, whereas the association with adenocarcinoma is much less strong (Doll, Hill, and Kreyberg, 1957; Kreyberg, 1962; Wynder, Mabuchi, and Beattie, 1970; Kreyberg, 1971). Kennedy (1973) found that smoking had little influence on the histology of lung cancer in British women, while a weak and non-significant correlation only between smoking and Kreyberg group I tumours in British women was found by Doll *et al.* (1957). Hanbury (1964), and Ashley and Davies (1969). Among the 4000 cases reported from Scotland by le Roux (1968), one-third of the non-smokers had squamous-cell carcinomas. On the other hand, recent large series from America show a strong and significant correlation between smoking and Kreyberg group I tumours in both sexes (Vincent *et al.*, 1965; Wynder *et al.*, 1970). Kennedy (1973) concludes that Kreyberg's hypothesis concerning the connection between group I tumours and environmental carcinogens is valid for British men (Doll *et al.*, 1957; Kreyberg, 1962), Norwegian men (Kreyberg, 1962), and American men and women (Haenszel *et al.*, 1958; Vincent *et al.*, 1965; Wynder *et al.*, 1970) but not for British women (Doll *et al.*, 1957; Hanbury, 1964; Ashley and Davies, 1969; Kennedy, 1973). He wonders if British women are exposed to some unidentified environmental hazard responsible, at least partly, for group I tumours, so that smoking has little influence upon the type of tumour found. In the writer's series of women from Wales, there is a significantly higher incidence of non-smokers and a somewhat higher incidence of light smokers (less than 10 cigarettes per day) among women with adenocarcinomas than among those with epidermoid or oat-cell carcinomas (Table III).

The writer concludes that the incidence of cancer of the lung in men and women is influenced by sex and nationality, but that the role of environmental factors, including tobacco, in women is obscure and may vary in different parts of the world.

As a result of this study it can be concluded that in Wales the prognosis of cancer of the lung is far worse in women than in men, irrespective

of treatment. The average period of survival without treatment in the present investigation was only 4.8 months. For palliative deep x-ray therapy the average period was 3.5 months, for chemotherapy 4.7 months, and for radical deep x-ray therapy 9.2 months. Few women in any of these groups survived 12 months. The average survival period after poudrage for malignant effusion was only 4 months and that after thoracotomy was 4.4 months. The five-year survival rate after resection was only 14.3%, and this becomes only 11.4% if the patient dying after five years one month is excluded. The five-year survival rate after resection in women in this series is less than one-half of that in men.

A possible reason for the poor prognosis in women is the higher percentage of oat-cell tumours in women as compared with men, which has been found by a number of workers. In this series, 32% of tumours were oat-celled as against 29% epidermoid tumours. This sex difference in cytology is well shown in the paper by Goldman (1965; Table I). Squamous-celled tumours occurred in 39.3% of males but in only 11.4% of females, whereas oat-celled tumours occurred in 20.1% of males as against 52.3% of females. This, however, does not appear to account for the gravity of cancer in the women studied since epidermoid carcinomata did no better, and adenocarcinomata only slightly better, than the oat-cell carcinomata. Only 6 of the 29 epidermoid tumours in the series of 132 women were resectable, and only one of these survived for five years. The grave prognosis of the women in this series appears to be independent of the histology of their growths, although the sole long-term survivor who received no treatment had a well-differentiated epidermoid carcinoma. These findings correspond with those of Boucot and Percy (1960) in the USA and Merlier *et al.* (1969) in France.

The average age of the women in this series is almost identical with that of men in this region (South Wales). The figure for 214 men operated upon consecutively by the writer during a slightly earlier period was 57.5 years, while that for these women was 58.4 years. Age is, therefore, unlikely to have influenced the mortality unfavourably for women as compared with men. The location of the growths also did not differ significantly in women in this region.

Thirty of the women in the series of 132 had their growths resected, a percentage of 22.7. This corresponds with the resectability rate of about 20% of cases of cancer diagnosed irrespective of sex (*British Medical Journal*, 1975). Thirty of the

37 women submitted to surgery had their growths resected, a percentage of 81.1. This figure is in close accord with that given by Belcher and Anderson (1965), who found that resection was possible in 79% of 1134 operations (irrespective of sex). It thus appears that the poor prognosis in this group of women is not accounted for by an unduly low resectability rate as compared with cancers in a mixed series composed predominantly of men. Some other workers have also found resectability rates in women similar to those in men (Boucot and Percy, 1960; Ederer and Mersheimer, 1962; Watson and Schottenfeld, 1968); while others have found the rates to be lower in women (Nicholson, Fox, and Bryce, 1957; Ashley and Davies, 1969; Merlier *et al.*, 1969).

There appears to be a considerable difference of opinion regarding the outlook for women as compared with men in different countries. Ashley and Davies (1969), in the only other paper from Wales known to the writer on the subject of cancer of the lung in women (83 cases), found that, compared with men, cancer in women was less well differentiated, less likely to be squamous, less likely to be resectable, and more likely to have extrathoracic metastases at the time of diagnosis, and that the prognosis was poorer. My findings are similar. The resection rate for their women was 13.4%, as compared with 21% for men, and the incidence of extrathoracic metastases at the time of diagnosis was higher. These two studies seem to confirm that in Wales cancer of the lung is more serious in women than in men.

In England Nicholson *et al.* (1957) found a poorer prognosis in women than in men, and attributed this to the higher proportion of poorly differentiated tumours and the lower percentage of squamous-celled ones. Their series was composed of 910 patients, 70 of whom were women. Resection was possible in only 7% of women as against 21% of the whole series, and the three-year overall survival rate for women was only 1.9% as against 6.1% for the whole series. Bignall and Martin (1972) found the survival rates for women lower in all age groups, in those with squamous and undifferentiated tumours, in those who had resection or deep x-ray therapy, or neither, and in those with short or long histories, but none of these differences was statistically significant. The overall five-year survival rate for women was 4.3% and for men 5.8%. The comparative five-year survival rates after lobectomy were 24.2% and 26.5% and for pneumonectomy 11.8% and 16.6%. Hanbury (1964) reported on 100 women with histologically proved cancer of

the lung observed between 1948 and 1962, of whom 17 were treated by pneumonectomy and 10 by lobectomy. Only three of these patients survived five or more years.

In the USA the situation seems to be more favourable for women. Ederer and Mersheimer (1962) investigated 7547 white men and 1260 white women diagnosed between 1950 and 1959 in 99 hospitals in the USA and considered that the best method of expressing survival was by means of the relative survival rate. This was computed by dividing the crude (observed) survival rate, expressed according to the life table method, by the expected survival rate obtained from US life tables. This relative survival rate allows for age, sex, and year of diagnosis, and for all the material to be used. They divided their cancers into three stages, namely:

- Stage I Localized disease. The cancer is confined to its site of origin.
- Stage II Regional spread. The cancer has passed the bounds of the site of origin. The furthest spread is thought to be limited to neighbouring organs or tissues, or to regional lymph nodes.
- Stage III Distant or remote spread. The cancer has spread to organs or tissues beyond those immediately draining or bordering the site of origin.

There was no sex difference in the incidence of staging so that the carcinomata appeared to be equally aggressive in the two sexes. The overall five-year relative survival rates were markedly better for women than for men in stage I, but the advantage disappeared in stages II and III and was not apparent when all cases were considered collectively. Their findings were as follows:

Stage	Overall % Five-year Relative Survival Rate	
	Men	Women
I	20	41
II	6	7
III	1	1
All stages	9	10

When the results of surgery were analysed there was a highly significant difference, favouring women, in the five-year relative survival rate after resection in stage I and a better, but not significantly so, survival rate after resection in stage II. The figures for stage I were 35 and 68%, and for

stage II 13 and 20%. The improved survival in women was not explained by operative mortality, age, histopathology, location of the neoplasm, or the proportions of stages. The authors concluded that a sex-associated factor might inhibit tumour spread in women, especially while the disease remains localized. The findings of Connelly, Cutler, and Baylis (1966) were very similar to those of Ederer and Mersheimer (1962).

Watson and Schottenfeld (1968), also working in the USA and using the same methods of staging and of expressing the five-year relative survival rates as Ederer and Mersheimer (1962), found very similar survival rates to the latter authors in 3124 patients. There was very little difference in the overall survival rate between men and women. Between the years 1949 and 1955 the rates for men and women were 5.6 and 4.4% respectively, and between 1956 and 1962 3.9 and 4.5%. For the entire period 1949 to 1962 the five-year relative survival rate for men with localized disease (stage I) was 17.0% and for women 17.9%. There was no essential difference between the sexes with regard to staging, so that the aggressiveness of the cancers in the two series was similar. For the whole group of surgically treated cases there was very little difference between men and women in the five-year relative survival rate, but after surgery in stage I the women did significantly better, as shown:

	% Five-year Relative Survival Rate	
	All Stages	Localized
Men	17.2	29.1
Women	26.5	48.8

These figures confirm the opinion of Ederer and Mersheimer (1962) that the prognosis after resection for localized cancer is significantly better for American women than for American men. Jackson *et al.* (1969) and the California Tumor Registry (1963) also state that the prognosis is better in women than in men. On the other hand, Eisenberg *et al.* (1964), in a series of more than 4000 cases, found that during the period 1935 to 1949 the survival rate for women was higher than for men, but from 1950 to 1956 the rates were almost the same in the two sexes, while Boucock and Percy (1960) reported that 77% of their 104 women were dead in one year and that only 3% of them survived for five years. These figures represent a lower survival rate than overall figures from the literature at that time. The resectability rate of 27% was very similar to that of a consecutive

utive series of men in the same locality, namely 29%. Of the 28 women in the series of Boucot and Percy (1960) who had their growths resected, only three (10.7%) survived for five years, a figure very similar to mine.

In France, Merlier *et al.* (1969), reporting a surgical series of 89 cancers in women, of which 61 were primary and 28 were secondary, found that the thoracotomy rate was higher in women (42%) than in men (28%) and that the resection rate was correspondingly lower. Furthermore the five-year survival rate after resection was lower for women (16%) than for men (23%). However only 26 of the women whose growths were resected were followed up for five years or more, four of whom survived this period, so that the figures are small. During the period of the investigation 1279 men were submitted to surgery. Interpretation of the results is made difficult because both primary and secondary cancers of the lung and both sexes were included. The authors stated that histology had little influence on the results. The findings of Merlier *et al.* (1969) suggest that cancer of the lung in French women has a worse prognosis than in French men, but more information is necessary before a firm opinion can be formed.

Meyer and Berlinerblau (1964) reported 140 cases of cancer of the lung and pleura in women in France; six were primary, and three of these were mesotheliomata. Presumably most of their 64 cases of cancer of unknown origin, mostly adenocarcinomata, were primary, but their presentation makes impossible an assessment of the prognosis of primary cancer relative to that in men, and they make no reference to surgical treatment.

It thus appears that the prognosis for women with cancer of the lung is considerably worse than for men in Wales, somewhat worse in England, and possibly worse in France. Reports from the USA are conflicting, but the large series studied by Ederer and Mersheimer (1962), Connelly *et al.* (1966), and Watson and Schottenfeld (1968) indicate that the prognosis when the cancer is localized, and especially after resection in this stage, is significantly better for women than for men. The causation of sex differences in prognosis is obscure but is not explained by the age of the patient or by the histology, location, early aggressiveness or resectability of the growth. It would appear that some sex-linked factor must be operative.

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REFERENCES

- Ashley, D. J. B. and Davies, H. D. (1969). Lung cancer in women. *Thorax*, **24**, 446.
- Beamis, J. F., Jr., Stein, A., and Andrews, J. L., Jr. (1975). Changing epidemiology of lung cancer: increasing incidence in women. *Medical Clinics of North America*, **59**, 315.
- Belcher, J. F. (1971). World-wide differences in the sex ratio of bronchial carcinoma. *British Journal of Diseases of the Chest*, **65**, 205.
- Belcher, J. R. and Anderson, R. (1965). Surgical treatment of carcinoma of the bronchus. *British Medical Journal*, **1**, 948.
- Bignall, J. R. and Martin, M. (1972). Survival experience of women with bronchial carcinoma. *Lancet*, **2**, 60.
- Boucot, K. R. and Percy, H. (1960). Lung cancer in women. *Diseases of the Chest*, **38**, 587.
- British Medical Journal* (1975). Operability of lung cancer. (Leading article). **2**, 299.
- Burbank, F. (1972). U.S. lung cancer death rates begin to rise proportionately more rapidly for females than for males: a dose-response effect? *Journal of Chronic Diseases*, **25**, 473.
- California Tumor Registry (1963). Cancer registration and survival in California. *California Department of Public Health*, 1963, Berkeley.
- Christiansen, T. (1953). Primary epithelial lung tumours in autopsy material at Rikshospitalet, 1925-52. *British Journal of Cancer*, **7**, 428.
- Connelly, R. R., Cutler, S. J., and Baylis, P. (1966). End results in cancer of the lung: comparison of male and female patients. *Journal of the National Cancer Institute*, **36**, 277.
- Deaner, R. M. and Trummer, M. J. (1970). Carcinoma of the lung in women. *Journal of Thoracic and Cardiovascular Surgery*, **59**, 551.
- Deeley, T. J. (1975). Personal communication.
- Doll, R., Hill, A. B., and Kreyberg, L. (1957). The significance of cell type in relation to the aetiology of lung cancer. *British Journal of Cancer*, **11**, 43.
- Ederer, F. and Mersheimer, W. L. (1962). Sex differences in the survival of lung cancer patients. *Cancer*, **15**, 425.
- Eisenberg, H., Shames, J. M., Holloway, W. L., and Barrett, H. S. (1964). Cancer of the bronchus

- and lung: Connecticut 1935-1959. *Journal of Chronic Diseases*, **17**, 1033.
- Gentleman, J. F. and Forbes, W. F. (1974). Cancer mortality for males and females and its relation to cigarette smoking. *Journal of Gerontology*, **29**, 518.
- Goldman, K. P. (1965). Histology of lung cancer in relation to prognosis. *Thorax*, **20**, 298.
- Haenszel, W., Shimkin, M. B., and Mantel, N. (1958). A retrospective study of lung cancer in women. *Journal of the National Cancer Institute*, **21**, 825.
- and Taeuber, K. E. (1964). Lung-cancer mortality as related to residence and smoking histories. 11. White females. *Journal of the National Cancer Institute*, **32**, 803.
- Hanbury, W. J. (1964). Bronchogenic carcinoma in women. *Thorax*, **19**, 338.
- Jackman, R. J., Good, C. A., Clagett, O. T., and Woolner, L. B. (1969). Survival rates in peripheral bronchogenic carcinomas up to four centimeters in diameter presenting as solitary pulmonary nodules. *Journal of Thoracic and Cardiovascular Surgery*, **57**, 1.
- Jacobsen, A. (1953). Primary epithelial lung tumours in post-mortem material from Ullevaal Hospital (Oslo City Hospital). *British Journal of Cancer*, **7**, 423.
- Kennedy, A. (1973). Relationship between cigarette smoking and histological type of lung cancer in women. *Thorax*, **28**, 204.
- Kreyberg, L. (1959). Lung tumours: histology, aetiology and geographic pathology. *Acta Unio Internationalis Contra Cancrum*, **15**, 78.
- (1961). Relationship of different histological lung tumour groups to tobacco smoking. *British Journal of Cancer*, **15**, 51.
- (1962). Histological lung cancer types: a morphological and biological correlation. *Acta Pathologica et Microbiologica Scandinavica*, Supplement, 157.
- (1971). Comments on the histological typing of lung tumours. *Acta Pathologica et Microbiologica Scandinavica*, **79A**, 409.
- and Saxén, E. (1961). A comparison of lung tumour types in Finland and Norway. *British Journal of Cancer*, **15**, 211.
- Lancet* (1971). Mortality trends, **1**, 1138.
- Lemoine, J. M. and Fauvet, J. (1974). Les tumeurs bronchiques malignes des femmes. *Bronchies*, **24**(3), 162.
- le Roux, B. T. (1968). The influence of predominant cell type on the management and prognosis of bronchial carcinoma. *Scottish Medical Journal*, **13**, 84.
- Merlier, M., Goux, J. P., and Hummel, J. (1969). Les cancers bronchopulmonaires opérés chez la femme. *Poumon et le Coeur*, **25**, 455.
- Meyer, A. and Berlinerblau, R. (1964). Remarques sur le cancer broncho-pleuro-pulmonaire chez la femme (à propos de 140 cas). *Poumon et le Coeur*, **20**, 805.
- Nicholson, W. F., Fox, M., and Bryce, A. G. (1957). Review of 910 cases of bronchial carcinoma with results of treatment. *Lancet*, **1**, 296.
- Royal College of Physicians (1971). *Smoking and Health Now*, p. 60. Pitman, London.
- Spencer, H. (1962). *Pathology of the Lung*, Chapter 19. Pergamon Press, Oxford.
- Vincent, N. T., Satterfield, J. V., and Ackerman, L. V. (1965). Carcinoma of the lung in women. *Cancer*, **18**, 559.
- Watson, W. L. and Schottenfeld, D. (1968). Survival in cancer of the bronchus and lung, 1949-62: a comparison of men and women patients. *Diseases of the Chest*, **53**, 65.
- Wynder, E. L., Bross, I. J., Cornfield, J., and O'Donnell, W. E. (1956). Lung cancer in women: a study of environmental factors. *New England Journal of Medicine*, **255**, 1111.
- , Covey, L. S., and Mabuchi, K. (1973). Lung cancer in women: present and future trends. *Journal of the National Cancer Institute*, **51**, 39.
- , Mabuchi, K. and Beattie, E. J., Jr. (1970). The epidemiology of lung cancer. *Journal of the American Medical Association*, **213**, 2221.

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